An update on the role of membrane and soluble endoglin in vascular homeostasis

Carmelo Bernabeu

Centro de Investigaciones Biologicas, Consejo Superior de Investigaciones Cientificas (CSIC) and Centro de Investigacion Biomedica en Red de Enfermedades Raras (CIBERER), Madrid, Spain
E-mail: bernabeu.c@cib.csic.es

Endoglin is an endothelial membrane glycoprotein that acts as an auxiliary receptor for TGF-β and as a ligand for integrins. Mutations in the endoglin gene are responsible for a vascular disorder known as hereditary hemorrhagic telangectasia type 1 (HHT1) characterized by recurrent epistaxis, telangiectasia and arteriovenous malformations. Membrane bound endoglin is a proteolytic substrate of MMP14 resulting in the release of soluble endoglin, which is associated with systemic hypertension during pregnancy and contributes to the pathogenesis of preeclampsia. Because endoglin displays an RGD motif, which is a prototypic sequence involved in integrin-based interactions with other proteins[1], we have analyzed its adhesive role in the circulatory system. Adhesion between vascular endothelial cells and mural cells is inhibited upon suppression of endoglin or β1-integrin, as well as by addition of soluble endoglin, anti-integrin α5β1 antibody or an RGD peptide[2]. In HHT1 mice, endoglin haploinsufficiency induces a pericyte-dependent increase in vascular permeability and transgenic mice overexpressing soluble endoglin, an animal model for preeclampsia, show podocyturia, suggesting that soluble endoglin is responsible for podocytes detachment from glomerular capillaries[2]. In HHT, vascular injury has been postulated, among others, as a second hit necessary for the vascular lesions to appear. After endothelial injury, the transcription factor Kruppel-like factor 6 (KLF6) translocates into the cell nucleus to upregulate membrane endoglin and MMP14 expression[3,4], followed by the release of soluble endoglin. Overall, the current data suggest a critical role for membrane and soluble endoglin in vascular cell-mediated adhesion and provide a better understanding on the mechanisms of vessel maturation in the normal circulatory system, as well as in pathologies such as preeclampsia or HHT.

(1) Rossi et al. 2013. *Blood* 121:403-415; (2) Rossi et al. 2016. *Cell. Mol. Life Sci*. 73:1715-1739; (3) Botella et al. 2002. *Blood* 100:4001-4010; (4) Gallardo-Vara et al. 2016. *Angiogenesis* 19:155-171.